HORMONES
and
BODY WATER

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and
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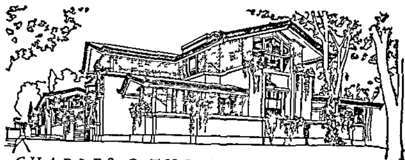
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Introduction

THE ENDOCRINE system in general is involved in the normal and pathological physiology of fluid metabolism This is clear from modern studies on such clinical entities as diabetes insipidus Addison s disease toxemias of pregnancy menstrual dysfunction and liver disease It is the purpose of this monograph to attempt a correlation of present knowledge of the role of internal secretions in such phenomena Much material basic to this discussion on non endocrine phases of the subject has been presented in earlier monographs of this series [81 88b]

The human body is composed of approximately 70 per cent water As a result of physicochemical forces this water is distributed in fairly definite amounts into two main compartments that which is inside body cells (intracellular fluid) and that which is outside the cells (extracellular fluid) The extracellular fluid in turn is subdivided into that present *in the blood (plasma) and that which is outside both* blood vessels and cells (interstitial fluid) including such minor reservoirs as the synovial cerebrospinal and intraenteric fluids

The physicochemical factors which determine this internal partitioning of body water will not be considered in detail here Mention should be made however of the conventional concept that the major influence holding water in the extracellular spaces is the osmotic pressure exerted by

the sodium salts sodium being limited largely to the extra cellular fluid as a result of cellular membrane phenomena Various additional influences, some of which are not well understood determine the partitioning of the subdivisions of the extracellular fluid For instance one long recognized factor by which the plasma fluid level is maintained, despite the fact that the hydrostatic pressure of the blood is tending to force water through the capillaries into the interstitial spaces is by the supplementary colloidal osmotic pressure exerted by plasma proteins Intracellular fluid volume is maintained by the osmotic action of substances more or less restrained by cell membranes to intracellular sites the most important of which are the potassium salts

These concepts are summarized herewith in a modifica tion of one of Dr J L Gamble s well known diagrams (Figure 1) They are useful generalizations but it should be remembered that as stated, they are oversimplified in that electrolyte and water distribution of tissues vary among themselves and in different physiological states [25]

The process of maintaining proper levels of the body fluids is inevitably complex because the rate of water and salt intake is erratic and its extra renal loss as by sweating is variable and relatively independent of the amounts of body water available

Fortunately the body can tolerate considerable variation in its total water content and the processes of adjustment to such variations although definite are sometimes slow Quick and viligant effort is made on the other hand to maintain constancy of other factors in the extracellular fluids such as hydrogen ion concentration and osmotic pres sure Regulation of osmotic pressure is achieved primarily by regulation of the rate of salt and water excretion

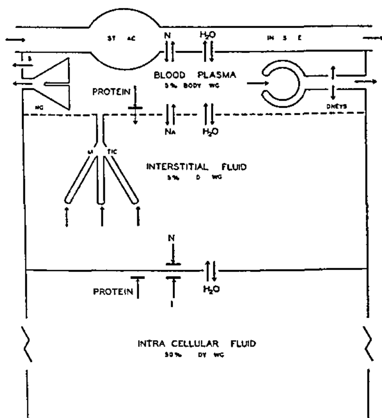


Figure 1 A diagram modified from Gamble illustrating some factors which vary and regulate the distribution of body fluids

Thus in the maintenance of a constant internal environ ment the kidney serves as keeper of the gate In the face of extra renal influences tending endlessly to vary the body content of salt and water it adjusts its rate of excretion of these substances to the end of maintaining a constant osmotic pressure Less sensitively thirst and salt appetite also help to maintain the *status quo*

2

Evolutionary Considerations

THE HUMAN BODY and its functional mechanisms are the end result of over 500 million years of evolutionary processes These processes could not be brought about by direct wilful change to meet adaptive needs They depended rather upon the survival of fortuitous mutations in the rugged contest of natural selection The inevitable consequence of such lack of teleological design is that the result will not be predictable and that it will likely be awkward or even bizarre While the evolutionary story of our body fluids and the organs which maintain them has been read only dimly such progress as has been made helps greatly in interpretation of events in the human body

It was one of the classic concepts of Claude Bernard[7] that the body cells of higher animals actually live and function in an aqueous internal environment and that the ability to maintain constancy of this internal fluid medium conveys to these organisms an independence in an unstable external environment which lower forms did not possess The living organism does not really exist in the *milieu exterieur* but in the liquid *milieu interieur* formed by the circulating organic liquid which surrounds and bathes all tissue elements The stability of the *milieu interieur* is the primary condition for freedom and independence of existence

The accessory concept that the fluid internal environment of vertebrates — the extracellular fluid — is only modified sea water maintained with the saline concentration which prevailed during the geological epoch in which their ancestors evolved was stated fully by Macallum[80] The lines of Wordsworth have been pharaphrased[3] as follows

Though inland far we be
Our blood has salt from the immortal sea
Which brought us hither

Since its original proposal this theory has received deferential treatment if not unequivocal verification The hypothesis of Macallum is based upon a striking similarity in electrolyte ratio and content between extracellular fluid and the more dilute seas of the early Paleozoic era, periods during which land forms are supposed to have arisen If this concept be true then not only do human body cells maintain a constant internal fluid environment but they maintain an environment to which their ancestors became adapted some 480 million years ago

The improvisations which animals used to maintain a constancy of the internal fluid environment in the face of radically different external environments makes one of the most fascinating stories to which the combined sciences of phylogeny and physiology have turned The story is far from complete in any particular but as regards the kidney available fact and intelligent speculation has been brilliantly recorded in the writings of Dr Homer W Smith[10] Vertebrate animals most evolutionists believe arose in fresh water as fish like forms from ancestors whose body fluids had been adapted previously to a marine existence To maintain a saline extracellular fluid in the face of the osmotic

inrush of water from a fresh water external environment imposed a serious problem They met this problem Smith believes, in two ways First, they acquired impermeable coats and thus provided a mechanical barrier to osmotic dilution This could only be a device of limited effectiveness because the problem of survival precluded covering the gills and mucous membranes, through which water could pass freely The armor typical of the fossilized vertebrates of the Silurian and Devonian periods is thought to bear witness to the attempted defense against the osmotic invasion of fresh water As a second attempted defense the circulatory system was connected to the kidney tubules by means of the glomeruli thus the organism was able to use the energy of the beating heart to pump water out as fast as it came in Smith feels that the fundamental architecture of the human kidney is based on its original adaptation to serve as a water pump

After having developed a functional water pump which served to offset the osmotic imbibition of water in a fresh water habitat the descendents of these early vertebrates migrated into many different environments In these new habitats they were confronted with new problems Some returned to the ocean but by this time the seas were saltier than before and hence were hypertonic to the body fluids Many adaptations appeared in an attempt to prevent dessication and to counteract the heritage of mechanisms designed to offset a constant osmotic inflow rather than outflow of water In sharks the renal threshold to urea was elevated to the end that enormous amounts of urea were retained in the plasma, thus equalizing the osmotic pressure of their body fluids with that of the hypertonic sea Other fish consumed salt water and distilled it by excreting the salt

through the gills and were thus able to resist dessication in a hypertonic environment As the glomerular filtering apparatus which evolved in fresh water was no longer an asset some forms became adapted to their hypertonic environment by reducing or obliterating the glomeruli of their kidneys and relying upon the tubular secretion of metabolites

Other forms migrated to terrestrial environments where they encountered habitats that varied from swampy regions to desert aridity The land vertebrates needing to conserve water so that they could leave their water sources and make the best use of their terrestrial domain employed various stratagems to maintain a constant extracellular medium The reptiles and birds modified their metabolic processes so as to excrete a supersaturated uric acid solution which precipitates in the cloaca From this site water could be reabsorbed and a relatively dry urine eliminated The adaptations which gave mammals their supremacy has made their problem of water conservation more difficult They developed along with the birds the trait of warm bloodedness which tends to increase evaporative fluid loss Further the higher metabolic rate associated with warm bloodedness results in the need for the excretion of more metabolites which carry out water as their solvent Those mammalian forms which help regulate their body temperature by panting or sweating place an additional strain on the water conserving mechanisms Blood pressure is high in mammals and that tends to filter more fluid through the glomeruli than would otherwise be the case And lastly the number of glomeruli is greatly increased thus making available a larger surface area for filtration The result of these factors is that in man some 125 ml of fluid is filtered into the renal tubules per minute most of which is and must be reabsorbed to avoid speedy

oblivion Thus it seems that the heart and kidney tubules are working against each other to provide the human body with an excretory mechanism which while it has the sub stantial merit of working remarkably well is from the stand point of energetics grossly inefficient Smith[10] evaluates it thusly There is enough waste motion here to bankrupt any economic system — *other than a natural one for Nature is the only artificer who does not need to count the cost by which she achieves her ends*

A portion of the fluid filtered into the renal tubules is reabsorbed passively along with its solutes In addition a new use of an old hormone that of the posterior pituitary gland appears in its full blown form in the mammals This hormone stimulates a further reabsorption of water from the tubular fluid and permits for the first time the excretion of a true hypertonic urine by this means a relatively effective conservation of water is achieved Nevertheless uncontrol able water loss is of *such magnitude as to make water the most immediately essential dietary constituent*

It is now clear that at some stage in these processes other hormones particularly *those of the adrenal cortex* entered the picture affecting the excretion of both salt and water The cortical hormones tend to inhibit sodium excretion and enhance the excretion of potassium Could this action be an adaptation to the relatively low sodium and high potas sium diet of the animal that departed from the salty sea first to fresh water and then to the equally salt poor land? No evidence is at hand on which to base an answer but the peril risked by the wild animal in search of salt and the avidity with which man adopts the salt shaker point to the adaptive significance of such mechanisms

The comparative physiologist has an inviting task before

him — that of writing the role of endocrine agents in this panoramic series of evolutionary events At the moment it is except as regards the posterior pituitary essentially an untold story

3

The Posterior Pituitary Antidiuretic Hormone

THE POSTERIOR LOBE of the pituitary gland (neurohypophysis) secretes one or more hormones It is possible for the chemist to fractionate posterior pituitary extract into two almost pure polypeptides — one *pitressin* (vasopressin) which elevates blood pressure and reduces the renal excretion of water and a second *pitocin* (oxytocin) which stimulates uterine contractions The unfractionated water soluble extract of the posterior pituitary is generally designated as *pituitrin* Dr John J Abel[1] long maintained that the fractionation of posterior pituitary extract first achieved by Dr Oliver Kamm and associates[65] represented a chemical artifact and that one mother molecule exhibiting all of the activities was actually secreted into the blood stream Powerful support of this concept comes from the more recent work of van Dyke and associates[123] who purified one large protein molecule which through all stages of purification retained constant ratios of pressor antidiuretic and oxytocic activities Of the many actions exhibited by neurohypophyseal extracts completely convincing evidence attaches physiological significance only to its effect on the excretion of water by the kidney Verney[1, 5] showed that a perfusate of a head heart lung kidney contained something lacking in heart lung kidney perfusates which caused the secretion of a hypertonic urine The pitressin fraction which exerts this effect is generally spoken of as the *antidiuretic hormone* or ADH A wealth of evi

dence from many sources has shown that the primary action of ADH is to stimulate the reabsorption of water from the distal portion of the kidney tubule and perhaps simultaneously to enhance the excretion of sodium and chloride

The condition of diabetes insipidus due to inadequate secretion of ADH is characterized by the excretion of great volumes of dilute urine and a consequent driving thirst that to prevent dehydration may require the consumption of large amounts of water Diabetes insipidus can be produced experimentally and studies have shown that without ADH an organism cannot excrete a urine that is hypertonic to the blood plasma Therefore the consumption of any substance which has to be excreted in addition to normal urine solids demands the excretion of extra amounts of water and hence exaggerates the diabetes insipidus state

The physiological significance of ADH and the regulation of its secretion was long obscured by the fact that lesions of the hypothalamus could cause a diabetes insipidus apparently identical with that resulting from damage to the neruohypophysis This dilemma was clarified by the work of the late Dr S W Ranson and collaborators at Northwestern University work which culminated in the monograph *Diabetes Insipidus and the Neuro Hormonal Control of Water Balance*[85] This was a remarkably enlightening document and established the fact among other things that the posterior pituitary is controlled by centers in the hypothalamus Injury to these hypothalamic controlling centers or to the fiber tracts between them and the posterior pituitary or to the latter organ itself all had the same effect they shut off the supply of ADH and resulted in diabetes insipidus

With the above facts established study then turned to the question of what physiological factors regulated the

hypothalamus and indirectly regulated the rate of ADH secretion Gilman and Goodman[48] demonstrated that ADH secretion as determined by amounts of antidiuretic material appearing in the urine, was increased in dehydrated states This and other related work permitted a rational linking of known facts leading to the conclusion that in water deprivation the hypothalamus is stimulated, ADH secreted, the kidney induced to excrete a more concentrated urine and water conservation thus effected Apparently the opposite occurs when water is available in excess, the ingestion of water shuts off the ADH output giving rise to a water diuresis which has been aptly termed a physiological diabetes insipidus (Verney[126])

Studies attempting to identify the specific stimulus to which the hypothalamus responds under conditions demanding maximal water conservation were initiated in this country and in England The experiments of Hare and associates[27] and Verney[126, 127] led to the concept that osmoreceptors in the hypothalamus respond to an elevated osmotic pressure of the blood by stimulating the neurohypophysis Verney, for instance, showed that proper doses of hypertonic solutions injected into the carotid artery and hence reaching the hypothalamus in a relatively undiluted condition would cause release of pituitary ADH If the same solution was injected into the jugular vein and was consequently well diluted before reaching the hypothalamus no stimulation of the posterior pituitary resulted

We have then a neuro humoral mechanism that is apparently exquisitely sensitive to variations in water load as reflected by blood dilution which operates to maintain the stores of body water at optimal levels There are in addition however other possible regulatory mechanisms which could control the effective amounts of circulating ADH by con

trolling its rate of destruction in contrast to its rate of secretion In studies subsequently described (Section 10), it has been demonstrated that the liver inactivates administered pituitary ADH The hepatic inactivating agent is an enzyme, the activity of which varies in different pathological states The full significance of such findings remains to be determined In addition to the factors just mentioned it is known that neurogenic stimuli [19, 54, 88] for instance painful stimuli and probably a variety of drugs cause a release of ADH and consequent antidiuresis The adaptive value of such mechanisms is obscure

The effect of posterior pituitary hormone on electrolyte excretion is not as well understood as is its effect on water excretion An abundance of evidence has shown that while decreasing the excretion of water posterior pituitary extracts increase the output of sodium and chloride under most physiological conditions [43, 95] As simply stated the rationale of such an effect would seem obvious to restore a hypertonic blood to normal the most effective means would be to retain water and release salt The situation may be more complicated however sodium chloride and water are generally either retained or lost together Full interpretation of these phenomena must take into account the actions of the hormones of the adrenal cortex as discussed below Furthermore while the pharmacological evidence is clear that posterior pituitary hormones can increase sodium and chloride excretion there is a paucity of physiological evidence showing that they actually do so under ordinary conditions Critical data on the point would be highly welcome In some species at least question has been raised as to whether the same posterior pituitary hormones that cause antidiuresis are the stimulants of salt excretion [58]

a Interrelationship of the Anterior and Posterior Pituitary

The clinical observations of von Hann [128] led her to the conclusion that maximal diabetes insipidus developed only when the posterior pituitary was incapacitated and the anterior pituitary functional The experiments of Curt Richter [93] and others have verified that viewpoint Although there may be some species differences in details, it is generally true that the usual type of total hypophysectomy, involving removal of the anterior and most of the posterior lobe, leads only to a mild diabetes insipidus which soon subsides to negligible proportions Full fledged diabetes insipidus occurs only when the anterior lobe is undisturbed [85] Water metabolism is not normal, however, in hypophysectomized animals since animals without ADH cannot excrete a concentrated urine and do not show a normal diuretic response when excess water is ingested [43]

This raises the question as to whether there is a specific anterior lobe diuretic hormone which balances the action of posterior pituitary ADH All workers are in agreement that no such diuretic hormone has been found and although details are obscure it is all but certain that the diuretic influence of the anterior pituitary results from the cumulative action (Figure 2) of several of its known hormones [43] These include the adrenocorticotrophic hormone (ACTH) which stimulates the production of cortical steroids without which a high rate of water excretion cannot occur (see Section 4), also involved is the action of thyrotrophin which stimulates the production of thyroxine a known diuretic agent the pituitary growth hormone, by maintaining appetite and certain aspects of metabolism results in the production of

metabolites which demand water for excretion and hence enhance urine volume lastly, some pituitary factors are necessary for the maintenance of normal renal clearances and presumably for the maintenance of diuresis[1 9]

The hypofunction of the adrenal cortices of hypophysec tomized animals can account in part for their inability to

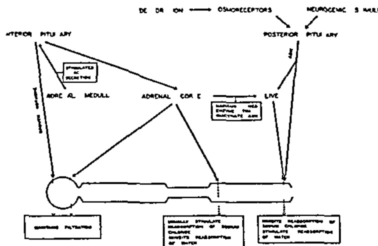


Figure 2 A diagram illustrating possible interaction of various hormones in the control of salt and water excretion.

excrete administered water at a normal rate it cannot ac count entirely for the deficient glomerular filtration rate of such animals[18]

b Summary

The posterior pituitary gland is the source of an anti diuretic hormone which acts upon the kidney tubules to stimulate the reabsorption of water The posterior pituitary is stimulated to secrete ADH when there is need for water conservation by an increase in the osmotic pressure of the

blood reaching osmoreceptors in the hypothalamus The condition of diabetes insipidus is due to an inadequate secretion of ADH The full fledged condition is only seen when there is a functional anterior pituitary present. The latter probably exerts its effect by the cumulative action of several of its known hormones which cause increased food intake, increased metabolisms, maintain glomerular filtration and inhibit the renal tubular reabsorption of water

4

The Adrenal Cortex

IN THE EARLY 1930s after the preparation of the first potent extracts of the adrenal cortex, knowledge of the long mysterious function of that gland began to unfold[45] The first clearly recognized func tion and for a while mistakenly thought by many to be the paramount function of the cortical hormones was a role in electrolyte and water metabolism

The early work of Loeb Harrop Swingle Kendall, Zwemer and others showed that in adrenal insufficiency there was a fall of plasma sodium and chloride due to a renal loss of these ions[53 65 110] This was associated with a retention of potassium[13] The importance of the sodium loss could hardly be gainsaid in view of Loeb s demonstra tion[77] following the less conclusive work of others that the administration of NaCl maintained life if not a normal state in the absence of the adrenals The best substitute for cortical hormones as shown particularly by Allers and Ken dall[2] was a high sodium low potassium diet

The renal loss of sodium in adrenal dysfunction is asso ciated with a renal loss of water but not one adequate to explain the hemoconcentration and extracellular dehydra tion of that syndrome The term dehydration however is ill applied to the state of adrenal insufficiency The loss of extracellular sodium permits some renal loss of water but also permits cells to imbibe water osmotically so that most tissues studied show a higher water content than normal

and the total percentage of body water determined on a fat free basis, is unchanged by adrenalectomy (Harrison and Darrow [52]) There is then a relative extracellular dehydration and cellular dehydration

The work of Wintersteiner and Pfiffner Kendall Reichstein and others led to the crystallization of twenty eight steroids from adrenal tissue [53] No one knows how many of these are actually secreted as hormones into the blood stream Only a small number have known corticoid activity One *of them desoxycorticosterone, generally used as its acetate* (DCA), has been most extensively studied because of its easy synthetic production There is doubt however as to whether it is a true adrenal hormone [53] It is nevertheless, the most potent substance known in causing sodium retention and potassium excretion

A simple statement of the concept most widely held is that the cortical hormones cause a renal retention of sodium and water and a loss of potassium This is a misleading oversimplification Actually, the actions of cortical hormones in such phenomena are highly variable and few general rules can be stated except in terms of precisely defined experimental or clinical conditions One of several complicating features is that different types of adrenal steroids have different actions If to the desoxycorticosterone molecule one adds a hydroxyl or carbonyl group at carbon 11 and a hydroxyl group at carbon 17 a compound such as cortisone results This alteration of the steroid molecule endows it with remarkable potencies in carbohydrate metabolism in stress and in the treatment of diseases such as arthritis It becomes at the same time however less potent in causing sodium and water retention and in fact under some conditions this action is reversed [117, 43]

a Interrelation of Adrenal Cortical and Posterior Pituitary Hormones

It is highly probable, as indicated by modern work, that the alterations in electrolyte and water metabolism seen in adrenal insufficiency are not due entirely to lack of cortical hormone *per se* but in part to an unantagonized activity of the hormones of the neurohypophysis Corey Silvette and Britton [24] first proposed the theory of a physiological antag onism between the adrenal cortex and the posterior pituitary Their idea has been refined elaborated and its limitations indicated by others The most intelligible interpretation of adrenal cortical function however, is one that considers simultaneously the role of neurohypophyseal hormones (Figure 2)

b Sodium Metabolism

Unless a crisis of adrenal insufficiency is precipitated quickly as a result of stress it is usually associated with a fall of plasma sodium due largely to increased renal excre tion of this ion Although varied renal deficiencies may be present convincing studies have shown that sodium is lost because it is not reabsorbed in normal amounts from the glomerular filtrate There is a curious exception to this statement It has been shown in adrenalectomized animals (Roemmelt *et al* [95]) that if the plasma sodium is elevated above normal by experimental means more sodium is re absorbed and less excreted from tubular urine than in nor mal animals The opposite occurs at normal or subnormal plasma sodium levels In other words in adrenal insufficiency sodium is lost when it needs to be retained and retained when it needs to be lost Although adrenal insufficiency is

seldom seen in conditions where the sodium load is high this observation is however of much theoretical interest It shows that sodium is not lost through the kidney because of any incapacity of that organ to do osmotic work without the aid of cortical hormones (in the sense that skeletal muscle cannot do its characteristic work without cortical hormones) It implies rather that the kidney tubule is usually inhibited in adrenal insufficiency from doing the customary amount of osmotic work in reabsorbing sodium from tubular urine If this argument be granted the question raised is that of the identity of the implied inhibitor

Posterior pituitary extract (pitressin) causes an increase in sodium and chloride excretion under almost all conditions observed It does so by inhibiting the tubular reabsorption of those ions If both cortical hormones and pitressin are injected simultaneously, they tend to antagonize each other[105] In adrenal insufficiency the sodium excreting effect of pitressin would be unchecked Furthermore, it has been shown in the author s laboratory and elsewhere that pitressin or a substance with similar properties actually accumulates in body fluids after adrenalectomy[9 11 13 75 8] Winter Ingram and Gross[130] showed that the plasma sodium level does not fall in adrenalectomized cats when the neurohypophysis was inactivated by hypothalamic lesions It can be said therefore as a reasonable hypothesis that when unchecked by cortical hormones ADH inhibits the tubular reabsorption and thus increases the excretion of sodium and chloride[95]

Interpretations of the effects of cortical hormone overdosage on sodium metabolism in normal individuals are less readily made at present DCA usually causes sodium retention of a marked sort but in certain unusual circumstances it

can even enhance sodium excretion Its effects are more pronounced after adrenalectomy when other steroids are not present The adrenal steroids oxygenated at carbons 11 and 17 (cortisone etc) may cause transient rises in sodium excretion and can antagonize under some conditions the sodium retaining effects of DCA Usually, and particularly after chronic administration they cause some sodium retention The mechanism by which these different and reversible effects[43] are obtained are not clear and it is not known that the posterior pituitary is involved Conn[23] has found that the sodium chloride content of sweat is high in Addisonian patients and in normal individuals is reduced by either DCA or ACTH The physiological significance of this interesting observation is yet to be assessed

c Water

There are two aspects to the action of cortical hormones on water metabolism which seem at first glance to be mutually contradictory In a sense there is a self contained antagonism in the properties of cortical steroids which results in some conditions in their causing water retention and in other conditions in their stimulation of water diuresis (Figure 3)

By theory whenever the cortical hormones cause sodium retention they should cause an osmotic retention of extracellular water This has in fact been seen in many circumstances When cortical hormones are lacking extracellular dehydration (but as noted earlier not a loss of total fat free body water) has long been recognized as a symptom of the adrenal insufficiency syndrome This dehydration develops concomitantly with the renal loss of sodium and is due partly to renal loss of water and partly to a shift of extracellular fluid to intracellular sites Re

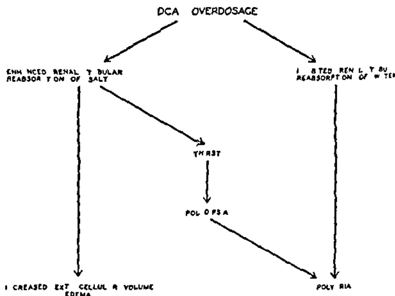


Figure 3 Illustrating the different actions of desoxycorticosterone which depending on variable physiological circumstances may result either in water retention or polyuria or both As a result of these influences prolonged administration of DCA may induce a diabetes insipidus-like syndrome

placement therapy reverses this tendency and overdosage particularly with DCA leads readily to edema formation in Addisonian patients It is much less likely to do so in normal individuals[103] a fact which implies an antagonism between the different cortical steroids in such phenomena When small doses of water are administered by mouth either to normal or adrenalectomized animals DCA can cause more sodium and water to be reabsorbed from the kidney tubules than would otherwise be the case and hence can cause some inhibition of the expected diuresis (Sartorius[106])

On the other hand, there are a large array of circumstances in which the cortical hormones stimulate water diuresis and promote water loss[4] (Table I) In this phe

TABLE I

CONDITIONS IN WHICH CORTICAL HORMONES AUGMENT THE DIURETIC RATE IN ANIMALS *

FLUID GIVEN AND ANIMAL USED	DCA *Chronic Treatment*	ADRENAL CORTICAL EXTRACT
Water *ad lib* in normal rats	+	+
Saline *ad lib* in normal rats	+ +	?
	Acute Treatment	
Excess hydration in normal rats	+	+ +
Mild hydration in normal rats	+	+
Slight hydration in normal rats	o	?
Mild dehydration in normal rats	o	+
Normal Saline in normal rats	o	+ +
Mild hydration in hypophysectomized rats	+	+ +
Mild hydration in hereditary dwarf mice	o	+ +

* T bl modifi d f m that of Gaunt B rn Boss E e le s d O born[42]

nomenon cortisone and its relatives are distinctly more active than DCA although all cortical substances tested are effective[8] This is best seen in water loaded animals where a dramatic protection against water intoxication can be demonstrated[89] or after prolonged administration of hormone which can result in a diabetes insipidus like syndrome[69] Conversely there is an almost complete and almost invariable inability of the animal or patient with adrenal insufficiency to increase its urine volume after the ingestion of water[43 94] This fact is the basis of the Robinson Powers Kepler water test for adrenal insufficiency[73 94]

It is clear that the cortical hormones are potent diuretic agents They will exert a diuretic effect except under circum

stances where their sodium retaining effect is of such magnitude as to prevent diuresis

The reason for the loss of the diuretic response to water in adrenal insufficiency and the enhanced diuresis after cortical hormone overdosage have been clarified considerably by work recently reviewed[42] In adrenal insufficiency water cannot be excreted at a normal rate primarily because it is reabsorbed from kidney tubules at an enhanced rate A reduced renal plasma flow and glomerular filtration rate may be contributory but not essential factors[16 17 79] Deficiencies in the intestinal absorption of water and other extra renal influences can be demonstrated but also are usually not of great importance

The accelerated reabsorption of water from renal tubules is probably due to an increased sensitivity to and increased blood levels of pituitary ADH The reasons for the accumulation of ADH in adrenal insufficiency are not entirely clear It is not likely the result of increased rates of secretion of this hormone It may however well be due to decreased rates of inactivation of ADH The liver as subsequently discussed is apparently a major site at which circulating ADH is destroyed This destruction is effected by an enzyme system which is dependent on adrenal cortical hormone for its normal activity Hence ADH may accumulate in adrenal insufficiency because of decreased destruction rather than overproduction In sum total the inability to excrete water possibly like the inability to conserve sodium is due in part to an unimpeded activity of posterior pituitary hormone

As would be expected from the nature of events in adrenal insufficiency an inhibited tubular reabsorption of water is the immediate cause of the enhanced diuresis which follows cortical hormone overdosage in intact animals[17]

This action however is not due to any decrease in the amounts of circulating ADH[17] and understanding of its ultimate cause requires further study

Lloyd and Lobotsky[75] have correlated the antidiuretic activity (presumably ADH) of blood with corticoid excretion in a wide variety of clinical conditions They find diuresis associated with a high ratio of corticoid to antidiuretic substance and vice versa

d Potassium

An increased excretion of potassium is one of the most invariable effects of overdosage with cortical hormones in normal individuals and potassium retention is usually associated with adrenal insufficiency This is just the opposite of the behavior of the sodium ion Potassium intoxication is presumably a contributory factor to death from adrenal insufficiency Despite the many established reciprocal relations between sodium and potassium in the body their excretion under the influence or absence of cortical hormones seem to be independent phenomena, not directly or casually related[95] The independent behavior of these ions may be due to the fact that they are under essentially different types of endocrine control While as indicated above the rate of sodium excretion is apparently determined by a balance between the antagonistic actions of adrenal cortical and posterior pituitary hormones the effect of these hormones on potassium excretion is similar rather than antagonistic They both increase potassium excretion and when given together their effects are additive[105] While the full physiological implications of these facts are yet to be explored a close correlation between potassium and sodium metabolism when endocrine factors are varied would hardly be expected

e Summary

. 1 Sodium and chloride excretion is generally inhibited by hormones of the adrenal cortex but under certain conditions that effect may be eliminated or reversed The posterior pituitary hormones stimulate sodium and chloride excretion under pharmacological conditions There is much logic in the suggestion that this depicts one of their physiological functions Many of the natural phenomena observed are most easily interpreted on the basis of an antagonistic interaction between the hormones of the adrenal cortex and the posterior pituitary Both exert their effects primarily on the reabsorption of sodium in renal tubules

2 Cortical hormones are diuretic agents and increase water excretion unless sodium retention is of such magnitude as to prevent this effect Their diuretic action is primarily due to the fact that they inhibit the tubular reabsorption of water, and thus antagonize the actions of ADH In adrenal insufficiency there is both a hypersensitivity to and an accumulation of antidiuretic agents thus accounting in large measure for the inability to excrete water normally

3 Both cortical and posterior pituitary hormones stimulate the excretion of potassium and there is no obvious causal relationship between the rates at which sodium and potassium are excreted in abnormal endocrine situations

5

The Thyroid

MOST HORMONES of the body affect water metabolism in one or another way Except for the hormones discussed above however the actions of most of these is probably incidental to other major functions Their effects, nevertheless can be dramatic and of major importance in abnormal clinical states

Thyroxin is a diuretic substance In acute experiments with animals both the diuretic response to administered water and the resistance to water intoxication is greatly augmented despite a reduced salt excretion [91] by treatment with thyroxin [44] In the human species on the other hand hyperthyroidism may retard the elimination of ingested water [73] This is perhaps due to adrenal cortical exhaustion [71] the diuretic effect of thyroxin is not manifested in animals with adrenal insufficiency [44]

When thyroid hormone is administered to myxedematous patients an appreciable diuresis is usually characteristic of the institution of therapy Boothby *et al* [14] attribute this to the rapid oxidation of deposit protein and the excretion of associated salt and water Normal subjects treated with thyroid hormone likewise show an increased diuresis but differ from hypothyroid patients in that the diuresis is of lesser magnitude and associated with a loss of potassium rather than sodium salts This finding is interpreted by Byrom [1] as indicating that in the normal subject the fluids leaving the body are of intracellular origin while those of the myxedematous patient are from extracellular sources

e Summary

1 Sodium and chloride excretion is generally inhibited by hormones of the adrenal cortex but under certain conditions that effect may be eliminated or reversed The posterior pituitary hormones stimulate sodium and chloride excretion under pharmacological conditions There is much logic in the suggestion that this depicts one of their physiological functions Many of the natural phenomena observed are most easily interpreted on the basis of an antagonistic interaction between the hormones of the adrenal cortex and the posterior pituitary Both exert their effects primarily on the reabsorption of sodium in renal tubules

2 Cortical hormones are diuretic agents and increase water excretion unless sodium retention is of such magnitude as to prevent this effect Their diuretic action is primarily due to the fact that they inhibit the tubular reabsorption of water, and thus antagonize the actions of ADH In adrenal insufficiency there is both a hypersensitivity to and an accumulation of antidiuretic agents, thus accounting in large measure for the inability to excrete water normally

3 Both cortical and posterior pituitary hormones stimulate the excretion of potassium and there is no obvious causal relationship between the rates at which sodium and potassium are excreted in abnormal endocrine situations

6

The Adrenal Medulla

ADRENAL MEDULLARY extract, like thyroxin can be a remarkably effective diuretic agent[46, 55, 107] Norepinephrine is more effective than epinephrine in this respect[83] In animals epinephrine induced diuresis can be of such magnitude as to lead to a transient dehydration while water is being administered at rates which normal animals cannot excrete[83, 46] Unlike thyroxin however epinephrine is not very effective in preventing symptoms of water intoxication This is probably due to the fact that it, again unlike thyroxin causes an increased salt excretion and thereby adds to the hypotonicity of extracellular fluids resulting from continued water administration[46, 107] Renal mechanisms involved have not been adequately studied The authors experience has been that these effects of epinephrine are seen only after large doses and that there are no comparable deficiency phenomena when the adrenal medullae are removed If this conclusion is correct — and there is lack of agreement on the point[107] — it would imply that the adrenal medulla is of little importance in the water metabolism of normal physiology The recent finding however that epinephrine inhibits the emotional release of antidiuretic hormone[127] suggests a hitherto unsuspected physiological role for this substance

Observations such as those mentioned above have yet to be correlated with others showing that epinephrine can re

Associated with the water retention characteristic of primary hypothyroidism there is a reduced excretion of sodium and chloride (Stephens[108]) Such is not true in cases of hypothyroidism due to pituitary dysfunction as here the secondary adrenal cortical deficiency results in sodium and chloride excretion (Means *et al*[86]) The administration of thyroid hormone will cause a return of sodium excretion to normal in primary hypothyroidism but will increase salt excretion in cases where pituitary dysfunction is involved

Significant alterations in plasma volume associated with myxedema and thyrotoxicosis have been reported In myxedematous patients and thyroidectomized animals there is a reduction in plasma volume[114, 116] with an associated increased concentration of plasma proteins In such cases the administration of thyroid hormone causes a return of the plasma volume to normal In thyrotoxicosis (Gibson and Harris[47]) the blood volume tends to be above normal

While the importance of the thyroid in the regulation of fluid metabolism is evident the mechanisms involved are obscure and probably largely indirect The effects on water metabolism are apparently in part secondary to effects on sodium chloride excretion In certain situations however, thyroxin may reduce salt excretion (after water administration) and in others increase it (in myxedema) Thyroxin also stimulates the adrenal cortex and thereby can affect water and salt metabolism although it has been shown that all of its actions are not mediated through the adrenals[44] Renal clearances of various kinds are altered by thyroxin[80, 88] It has recently been shown that thyroxin causes an increased renal plasma flow and glomerular filtration rate by activation of additional nephrons in the kidney[48]

7

The Pancreas

It is well known that in diabetes mellitus there can be a severe loss of electrolyte and water, and that the control of this factor is an important adjunct in diabetic therapy It is presumed however that these changes are secondary to glycosuria acidosis and other alterations in organic metabolism

When the blood sugar level is raised to a point where the glucose filtered exceeds the reabsorptive capacity of the renal tubules a glycosuria develops and water is carried out with the glucose[104] Thus the diabetic animal develops a polyuria which in turn causes a polydipsia This elevation in water exchange also tends to increase the amount of salt which leaves the body The process is exaggerated as the diabetes becomes more severe because ketone bodies are formed which are excreted in the urine These organic acids must be neutralized if the normal pH range of the plasma is to be maintained The neutralization is accomplished largely at the expense of sodium salts which when excreted further contribute to the demineralization of the body Associated with the excretion of the ketone bodies and sodium more water is lost Further complicating factors are overventilation of the lungs and vomiting All these factors lead to dehydration and hemoconcentration which together with the loss of salts results in an impairment of kidney function [104] This chain of events leads to changes in blood pH

duce urine volume[28, 97, 1, 1] A full understanding of the action of epinephrine on renal circulation would probably clarify the matter The observation that epinephrine can cause the release of pituitary ACTH[78] and hence stimulate the adrenal cortex probably can explain in part but not entirely its diuretic action

In proper experimental circumstances commercial epinephrine will increase the excretion of sodium and chloride markedly This action like the diuretic action of epinephrine is caused by its non epinephrine component[83]

8

The Gonadal Hormones

APPARENTLY all of the well known sex hormones have in common the property of causing a retention of sodium salts and water[118] In this respect they resemble their chemical relatives the adrenal cortical hor mones They differ from the cortical hormones however in that with the exception of progesterone they have not been shown to be diuretic agents under any circumstances studied[43] Progesterone might be expected to be an exception because it unlike other sex hormones can maintain life in adrenal ectomized animals Even so its diuretic properties are limited and much less marked than are those of the true corticoids The sex hormones probably have a corticoid like action in enhancing potassium excretion but that effect may be obscured if they induce sufficient nitrogen retention and general or localized growth to demand substantial amounts of potassium for tissue synthesis[66 87 116] Whether the sodium retaining effect of sex hormones is due in part to an action on the renal tubular reabsorption of this ion as is the case with the corticoids has not been clearly established that probably is the case Nevertheless actions at extra renal sites are likely of paramount importance One characteristic of the direct response of individual tissues and organs to sex hormones is a hyperemia and edematous hydration This is true of tissues such as the sexual skin of monkeys[68] and the uterus[1] This type of action can bind sodium and water

which are incompatible with consciousness and perhaps life itself (Figure 4) Replacement therapy which includes the administration of sodium bicarbonate and chloride is much more effective than insulin alone in the repair of the plasma structure and restoration of extracellular fluid volume

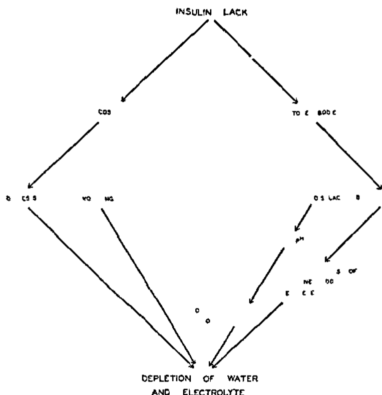


Figure 4. A diagram illustrating the factors initiated by lack of insulin which result in electrolyte and water depletion

9

Toxemias of Pregnancy

ONE OF THE CHARACTERISTIC features of the toxemias of pregnancy is a retention of sodium and water and a variety of hormones have been implicated as causal agents Fluid retention can occur, however without the appearance of toxic symptoms In fact an Addisonian like inability to excrete ingested water at a normal rate is characteristic of normal pregnancy although much more pronounced in pre-eclamptic or eclamptic patients[28, 101]

Several workers have suggested[101] that these changes in eclampsia are the consequence of high levels of estrogen and progesterone Such suggestions are based largely upon a questionable interpretation of the fact that there may be a decrease in the urinary excretion of these steroids Since both estrogen and progesterone are conducive to water retention such a theory would have considerable appeal On the basis of histological[112] histochemical[131] and chemical observations[101] there has developed however considerable evidence indicating an actual deficiency of estrogen and progesterone associated with toxemic pregnancy The failure of these steroids to appear in the urine is apparently not due to their renal retention but to their low level in the blood Thus the theory that excessive amounts of estrogen or progesterone are responsible for water retention seems to be untenable

Recent studies have been directed toward elucidation of

and reduce their excretion without any direct renal involvement A good part, therefore of the fluid retention induced by sex hormones represents a deposit of both intra and extra cellular fluid in selected organs as part of their normal responsiveness to the hormone in question

This does not eliminate the possibility, however, of renal effects or generalized effects on tissues not considered particularly responsive to sex hormones These are, in fact, suggested by the reputed decrease in blood volume after gonadectomy in man and animals[37] and by the frequent observance of a generalized edema following intensive treatment with sex hormones Some of these effects may be associated with changes in capillary permeability[86]

That such manifestations are not limited to experimental or pathophysiological circumstances is shown by the fact that definite changes in salt and water excretion result in increases of body weight during the menstrual cycle at the peak periods of estrogen and progesterone production namely, at the ovulatory and premenstrual periods[119]

is probably but not certainly posterior pituitary ADH The sum of all evidence certainly indicates the accumulation of some antidiuretic material or materials in the body fluids of eclamptic patients

In a discussion of the etiology of eclampsia Dieckmann *et al* [8] state Our preliminary studies seem to indicate that if there is a constant diuresis thus preventing any stimulus for the release of antidiuretic substance, the urine volume will remain fairly constant However, if the antidiuretic substance increases, there is a delay in the normal individual which becomes exaggerated in the toxemic patient, thus accounting for the oliguria or anuria Other factors may be involved in the decreased excretion of urine but it seems most probable that the antidiuretic substance is the important one

Explanations of the cause of water retention however, do not necessarily explain the cause of eclamptic convulsions unless those convulsions are due to water intoxication Dieckmann doubts that this is the case and on theoretical grounds one would not expect water intoxication to develop unless water was retained without equivalent amounts of salt (cf Section 12)

Another experimental approach to the problem is to compare the response of eclamptic and normal patients to the administration of antidiuretic hormone The administration of posterior pituitary extracts produced a greater decrease in urine volume and a greater increase in blood pressure in eclamptic patients than in normal pregnancy [8, 29, 61] In some cases convulsions were induced [29, 61] On the basis of other studies [8, 31] it is theoretically possible that the increased sensitivity to administered ADH is caused by a failure of the normal inactivation of antidiuretic hormone

the possible role of the adrenal cortical hormones in the eclampsias, but conclusive results are yet to be obtained The only evidence of adrenal hypofunction in the eclamptic syndrome is the report of reduced adrenal weight in some cases coming to autopsy [84] Normally both adrenal weight [101] and corticosteroid excretion are increased in pregnancy, and available evidence indicates still higher corticosteroid excretion in the toxemias of pregnancy [27, 78, 1 0] Since such findings could explain sodium and water retention and perhaps other symptoms, they have led Davis *et al* [27] and Garrett [88] to the conclusion that hypersecretion of one or another of the cortical hormones was a primary cause of eclampsia Moller Christensen,[88a] contrariwise suggests adrenal hypofunction as a more likely cause

Since the work of Anselmino *et al* [4] much attention has been given to the possible role of posterior pituitary like substances in toxemic cases The urine of pre eclamptic and eclamptic patients has been shown to contain comparatively large amounts of an antidiuretic substance [50, 67, 98, 111] which is present in greatest concentration at the height of the toxemia [67] The antidiuretic material is absent or present in smaller amounts in the urine of women with normal pregnancy [67, 111] Some investigators have considered this substance to be of posterior pituitary origin [111] while others report marked differences between it and posterior pituitary ADH [50, 98] It has also been demonstrated that the placentas of patients with toxemia of pregnancy contain larger amounts of antidiuretic material than do placentas from normal patients [50] Nothing is known as to the origin of this placental antidiuretic More recently Rienzo Lloyd and Hughes [98] have been able to detect an increase in the serum level of antidiuretic substance in eclamptic patients, a substance that

washes of animals with experimental cirrhosis suggesting a relationship between this hepatic vaso-depressor substance and the fluid retention accompanying cirrhosis

The presence of antidiuretic substances in the urine of patients with cirrhosis of the liver[92] and in the urine of rats with experimental liver damage has been demonstrated by Ralli and co-workers[72] The clinical findings have been confirmed by Drill and co-workers[49] It is possible that (1) these substances originate in the liver or (2) the anti diuretic substances, presumably from the posterior lobe of the pituitary are not effectively inactivated by a poorly func tioning liver thus making possible the full expression of their activity

The role of the liver in the inactivation of circulating posterior pituitary antidiuretic hormone has become well established since the finding of Heller and Urban[60] that homogenates of liver tissue rapidly inactivate posterior pitui tary extracts Both the *in vivo* and *in vitro* inactivation of posterior pituitary ADH have been demonstrated by Eversole *et al*[31] More recently it has been demonstrated that there is present in hepatic tissue an enzyme system which inacti vates posterior pituitary ADH and that in conditions such as adrenal insufficiency there occur alterations in the activity of this enzyme system[8] Lloyd and Lobotsky[76] found in creased serum titers of antidiuretic substances in patients with hepatic cirrhosis These results are consistent with the hypothesis of Ralli and co workers that at least in part the water retention seen in human liver disease is due to a de creased rate of inactivation of the antidiuretic hormone by damaged hepatic tissue It should be emphasized however that while the liver may be the most important site of in activation of the pituitary antidiuretic hormone it is not

10

The Liver

CLINICAL STUDIES of the past have led to the concept of an intimate relationship between hepatic and renal physiology particularly as regards electrolyte and water metabolism This is the basis of the ill defined and little understood term, the hepato renal syndrome Earlier workers (reviewed by Pick[90]) considered the liver to exert its influence on a mechanical rather than a humoral basis They visualized it functioning as a large reservoir collecting and reconcentrating the diluted blood which reaches it from the digestive tract

The basic fact of the problem is that there is a marked water and salt retention, sometimes involving ascites, associated with various liver diseases The fluid disturbances can occur with or without hypoproteinemia[70, 9] As early as 1926 evidence began to appear that the liver produced hormonal substances which play a role in water metabolism While the status of many of the hepatic preparations used is still a matter of question more recent studies indicate that under certain conditions substances which are capable of playing an important role in water metabolism can be identified Shorr, Zweifach and co workers[5, 100] have reported obtaining a vaso depressor and antidiuretic substance of hepatic origin (VDM) in animals suffering experimental shock This substance can be demonstrated in saline liver

11

The Adaptational Syndrome

MANY STIMULI which produce varying degrees of injury to an organism have been the subject of extensive study It is now well established that such injurious stimuli elicit the non specific reaction described by Selye[99] as the *adaptational syndrome* In the primary phase of the adaptational syndrome the subject may be in a state of relative adrenal cortical insufficiency If however exposure to the damaging agent continues for longer periods it passes into the resistant phase of the syndrome which is characterized by adrenal cortical hyperplasia and apparent increased cortical hormone secretion

The diuretic response elicited by certain non specific stress producing stimuli has been studied by Browne and co workers[20, 64] That the alterations in water metabolism can be correlated with the state of adrenal cortical activity has been strongly implied by Birnie and Eversole[10] When water is administered to animals immediately after exposure to a stress producing stimulus the rate of excretion is slower than normal This is probably due to either one or a combination of the following causes (a) a neurogenic release of ADH (b) alterations of renal circulation or (c) a transient adrenal cortical deficiency (Figure 5) The administration of adrenal cortical extract will prevent or minimize the anti diuresis If 24 or more hours are allowed to elapse between the application of the stress and testing a marked diuretic

the sole site All tissues studied (muscle, kidney, blood serum) contain inactivators of this hormone[81]

It is at least clear that, as in so many other aspects of metabolism, the liver occupies a central strategic position in the metabolism of inorganic constituents of the body

12

Water Intoxication

WHILE DEHYDRATION is a state to be avoided it is now well recognized that the forcing of water *per se* can be a dangerous procedure in many conditions[81] Among these are the endocrine deficiencies in which the mechanisms of water diuresis are disturbed The syndrome of water intoxication was named and described by Rowntree and co workers[96] It can be produced experimentally by forcing water by mouth or other routes and is characterized in its full blown state by convulsions of the *grand mal* type It is accompanied by electroencephlographic changes resembling those of epilepsy and epileptic seizures are themselves precipitated by hydration[85] Water intoxication is not a typical shock like state because blood pressure and peripheral circulation is well maintained[40 109] It is however accompanied by a profound fall in body temperature associated with a decrease in oxygen consumption a fact which can perhaps be in turn associated with a reduction of plasma chloride[40] Both plasma sodium and chloride are greatly reduced in water intoxication likely due more to their shift into the unabsorbed water of the gut and loss through the stream of water flowing through the kidney than to plasma dilution[40] The low plasma electrolyte levels permits absorbed unexcreted water to pass osmotically into cells there is no satisfactory evidence that plasma volume increases at all Water intoxication cannot be induced if NaCl

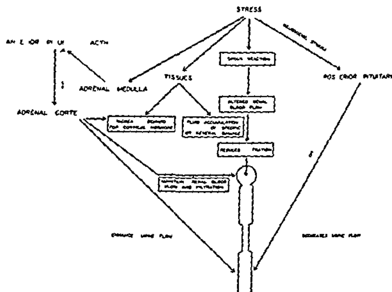


Figure 5 Illustrating an hypothesis which attempts to relate the various influences affecting fluid metabolism that are initiated by stress

In the early response to stress those influences tending to cause wa er retention are dominant as illustrated by a decreased diuretic response to water Secondarily even though the stress stimulus is repeated the accelerated activity of the pituitary adrenal cortical system may reverse the early changes This is manifested by an increased diuretic response to water If the cortical hormone output exceeds demand it will act back on the pituitary to shut off ACTH release thus serving as a self regulating mechanism

reaction is elicited This is associated with the increased adrenal activity and can be duplicated by the injection of cortical extract [10] in normal animals

It is of interest in this connection that animals can adapt themselves to high water loads by augmenting their normal maximal diuretic rate [74, 113] Thus, if rats are given increasing daily doses of water by stomach tube for a few days they are able then to excrete what would normally be an intoxicating water load without development of serious symptoms There is no good evidence that this adaptational phenomenon has an endocrine basis

12

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is given with excess water although the substitution of other solutes such as urea, which do not limit themselves to the extracellular fluid are of no protective value[51] This has led to the concept that the symptoms are due to cellular hydration, particularly the cells of the central nervous system While this interpretation is the best available at the moment, it could appropriately be subjected to further critical study

There is a marked susceptibility to water intoxication in adrenal insufficiency, in hypophyseal deficiency, after the administration of posterior pituitary extracts, and in any condition in which plasma sodium is reduced[41] Curiously, susceptibility is not increased in hypothyroidism[44] or in adrenal medullary deficiency[46] although the missing hormones in these states are both diuretic agents Cortical steroids have a high protective value against water intoxication both in adrenal and hypophyseal deficiency a protection only partly afforded by the fact that they stimulate diuresis They prevent water intoxication in part by extra renal influences which although definitely recognizable cannot as yet be clearly defined[12] In addition the cortical hormones protect normal animals against water intoxication so effectively that it is almost impossible to produce the condition if cortical hormone is administered with the water[39] The effective action of the hormones in normal animals unlike the situation in adrenal insufficiency is exerted almost entirely on the kidney and consists primarily of a stimulation of water excretion rather than a conservation of salt[43]

The therapeutic value of cortical hormones in states of excess hydration *is strongly suggested by physiological studies* but not amply demonstrated by clinical observation

13

Water Metabolism in the Newborn

During recent years it has become apparent that water and salt metabolism and renal functions in other respects differ profoundly in the newborn and the adult[83] In early life the ability is lacking to enhance the rate of excretion of salts and water when these substances are present in excess[59 84] Conversely there is an ineffective urine concentration of these materials when their intake is restricted and they need to be conserved The cause of the differences between the newborn and adult are not established although there are evidences of morphological immaturity in the newborn kidney[6] The subject is mentioned here because of the high probability that the differences are at least in part endocrine in origin The hormone content per unit weight of the posterior pituitary is very low in the newborn[58] and the responsiveness to the antidiuretic hormone is less than in adults[57] There is evidence that adrenal cortical function is not adult like at birth due to inadequate ACTH production[62] Some evidence suggests that there may be species differences in infantile adrenal function[62 1 4]

Heller s description of the way newborn rats handle water resembles strikingly the picture seen in adrenal and anterior pituitary insufficiency Osborn and LoCascio[89] in studies based largely on the rate of weight loss in hydrated newborn rats concluded that the administration of adrenal

is given with excess water although the substitution of other solutes, such as urea, which do not limit themselves to the extracellular fluid are of no protective value[31] This has led to the concept that the symptoms are due to cellular hydration, particularly the cells of the central nervous system While this interpretation is the best available at the moment, it could appropriately be subjected to further critical study

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The therapeutic value of cortical hormones in states of excess hydration is strongly suggested by physiological studies but not amply demonstrated by clinical observation

14

Conclusions

WATER is the most voluminous body constituent and the most immediately essential item of the diet Its metabolism is influenced in one or another way by most factors which influence protoplasmic activity As vertebrate animals have radiated into all environments they have carried with them a saline extracellular fluid as an internal environment The constancy of this internal environment as regards its electrolyte and water content is guarded primarily by the kidney The kidney in turn is guided in large degree by hypothalamic centers which control the posterior pituitary gland and by those factors largely working through the anterior pituitary which regulate the activity of the adrenal cortex In various indirect ways the hormones of the thyroid the adrenal medulla the pancreas and the gonads also become involved The state of pregnancy creates its own special problems and aberrations of fluid metabolism problems made the more confusing by the fact that the endocrinology of pregnancy is itself vastly altered from that of other states All tissues of the body serve as end organs for the interplay of hormones in such phenomena but the liver obviously occupies a site of strategic importance The full development of the regulatory system displayed is a postnatal phenomenon Despite much study details of the complex mechanisms involved are incompletely known in many respects but much progress in understanding has been made and more can be confidently anticipated

cortical extract stimulated water diuresis as it does in adults Their conclusion was confirmed by the work of Falk[31a] but not by work done in the laboratory of Professor Hans Heller[57a]

It is probable that those mechanisms involving the kidney hypothalamus, pituitary and adrenals are not functionally mature at birth nor for some time thereafter The problem of maintaining fluid balance in infants is, therefore different and more difficult than in adults,[83] and the procedures governing clinical practice in adults are obviously not entirely applicable to infants

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